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Lysergic Acid Derivatives

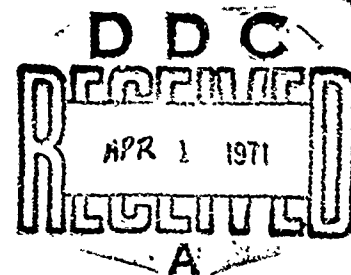
PROGRESS REPORT

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INTRODUCTION



The current project is to test the following hypothesis:

1. Do the psychotomimetic drugs cause paroxysmal, hypersynchronous activity in the rhinencephalic structures as reported in the previous work (reference--E.E.G. Journal, 9:623-642, November 1957) or is this a spurious finding related not to the psychotomimetic properties but to other factors--for instance, anti-serotonine activity, vegetative disturbances, or other physiologic processes as yet unknown but induced by agents with a similar chemical structure?

METHOD

Chronically implanted subcortical electrodes located in the septal, hippocampal, and caudate regions, as well as on the cortex, were placed in Macaca Mulatta. After standardizing the EEG response to d-LSD-25, these animals are being given a number of related compounds--such as isomers of d-LSD-25, compounds with substitutions in the indole nucleus and the various amides of lysergic acid. These derivatives of lysergic acid have varying anti-serotonine, psychotomimetic and visceral effects, as reported in an unpublished communication from the Medical Director of Sandoz Laboratories also. In order to

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clarify the importance of serotonin in inducing this subcortical, hypersynchronous activity, 5-hydroxytryptophane, which crosses the blood-brain barrier and is a precursor of 5-hydroxytryptamine, and phenylisopropylhydrazine, a monoamine oxidase inhibitor, were given alone and in combination. 1476 was also given.

The lysergic derivatives tried are as follows:

- d-LSD-25
- l-LSD-25 (no activity)
- BOL (no psychotomimetic activity, but anti-serotonine activity)
- ALD-52--l acetyl lysergic acid diethylamide (anti-serotonine effect equals d-LSD-25; psychotomimetic, 1/5-1/7 d-LSD-25)
- MLD-41--l methyl lysergic acid diethylamide (anti-serotonine effect greater than d-LSD-25; vegetative effects less; psychotomimetic effect similar to ALD-52)
- DAM-57--diethylamide of d-lysergic acid diethylamide (no psychotomimetic effect; weak anti-serotonine effect; strong vegetative effect)
- LSM (psychotomimetic effect 1/5 as strong as LSD)
- LAE--lysergic acid ethylamide (similar to d-LSD-25, but 1/20 as active)
- LPD-82--pyrrolidid of d-lysergic acid (no LSD effect, but autonomic effects)
- DLO-57--l-dihydro-lysergylamido-d-oxazolidone (hypotensive effect, but no psychotomimetic effect)

RESULTS

The EEG responses vary from monkey to monkey. Therefore, two things become apparent. These studies have to be done on a series of monkeys, and all the drugs should be given in sequence to one individual monkey. An attempt was made to first standardize their response, using d-LSD-25. By and large, it has been found that it takes at least 60 gamma per kilo to elicit the response in all monkeys. Occasionally at this level there will be no subcortical changes, although the reason for these rare exceptions will have to be checked after histologic studies on electrode placement, as in most instances it is effective. Also, we have found that there may be hippocampal effects

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without septal changes and vice versa. The hippocampus seems to be the most sensitive, but when the septal response is induced the over-all electrographic changes are more dramatic. Briefly, the studies that have been performed thus far are summarized in the chart below. The characteristics of the paroxysmal activity have varied considerably, but this cannot be analyzed with any meaning until further studies have been completed.

<u>DRUG</u>	<u>NO. OF STUDIES</u>	<u>DOSE RATIO</u>	<u>ELECTROGRAM</u>
d-LSD-25	12	-	Paroxysmal
l-LSD-25	2	3 times	No change
BOL	2	1 time	No change
ALD	2	3 times	Paroxysmal
MLD	2	3 times	Paroxysmal
LSM	2	3 times	Paroxysmal
DAM	2	1 time	Variable
LPD	1	1 time	Paroxysmal
5-HT	1	10 mg. per kilo	No change
PIH	1	5 mg. per kilo	No change
5-HT / PIH	1	"	Paroxysmal
EA-1476	3	250 gamma per kilo	Paroxysmal
Mescaline	2	15-30 mg. per kilo	Paroxysmal

OTHER STUDIES

The question arose as to whether d-lysergic acid diethylamide changed the blood-brain barrier so that compounds such as serotonin and adrenolutin would cross the blood-brain barrier. These studies, which were done under the

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direction of Dr. Heath, revealed that--unlike taraxein, which would change the blood-brain barrier, allowing these substances to go through--d-LSD-25 did not show the same effect, although Compound 888 did go through blood-brain barrier after previous medication with d-LSD-25.

FUTURE STUDIES

As already mentioned, the studies have to be repeated on a series of monkeys before the data can be meaningfully analyzed. It also seems imperative that the series of lysergic acid derivatives be given to individuals with some introspective ability who can report differences in the subjective sensations of these chemically related but pharmacologically quite different compounds. This latter study is now being initiated.

SUMMARY

Grossly, these preliminary studies suggest that there is a correlation between psychotomimetic drugs and rhinencephalic paroxysmal activity. One important observation is that in two of the three studies done thus far there occurred dramatic septal "spiking," as seen in schizophrenic patients after they have received 250 gamma per kilo EA-1176.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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